A Study of the Efficacy of MORAb-003 in Subjects with Platinum-Sensitive Epithelial Ovarian Cancer in First Relapse

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The objective of this study is to determine the efficacy of multiple intravenous infusions of MORAb-003 in platinum-sensitive subjects with a first relapse of epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) within...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON30586

Source
ToetsingOnline

Brief title
MORAb-003-002

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
ovarian cancer, Ovarian carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Morphotek, Inc
Source(s) of monetary or material Support: Morphotek;Inc.

Intervention

Keyword: Immunotherapy, Monoclonal antibody, Ovarian cancer, Recurrence

Outcome measures

Primary outcome

The endpoints are specific to each arm of this clinical study, because the clinical situation of a given subject dictates to which arm they are assigned and the therapy that they will receive. The primary variables to be measured are the indices of disease that defined the relapse in each individual subject; that is, the level of the biomarker CA125, with or without an objective measurement of tumor lesions by CT, MRI or other imaging modality, or physical examination with objective signs to follow.

The endpoint of the arm of asymptomatic subjects treated with single-agent MORAb-003 will be a reduction of CA125. The definition of a CA125 response is defined by the GCIC to be a 50% decrease, sustained for at least 20 days. [Duffy, 2005] If a subject in this arm also had measurable disease, that measure of disease will be followed (e.g. radiographic evidence will be followed by appropriate imaging techniques.)

The endpoints for subjects assigned to receive the standard chemotherapy regimen plus MORAb-003 (i.e. subjects with symptomatic disease and those without symptomatic disease who require immediate standard chemotherapy) will be A) CA125 according to the GCIG response criteria (Table 2), and B) objective measurement of tumor by the modality that defined that relapse. In most cases, this is anticipated to be radiographic studies interpreted by the RECIST criteria. The proportion of subjects attaining an objective rate of response

(CR or PR) and those achieving stable disease will be calculated.

In the third part of the study, subjects who attain CR or PR (or SD and an investigator*s assessment of a clinical benefit) with standard chemotherapy plus MORAb-003 and receive single-agent MORAb-003 maintenance therapy will be followed by CA125 and objective criteria. The length of second response will be measured and compared to the length of that subject*s first response.

Secondary outcome

To establish the serum pharmacokinetics of MORAb-003 in subjects with a low disease burden.

To determine the safety of MORAb-003 in combination with standard chemotherapy.

Study description

Background summary

MORAb-003 has the potential to be an effective agent against epithelial ovarian cancer, either alone or in combination with other drugs. MORAb-003 works by a different mechanism from other cancer therapeutics and has been shown to be well tolerated. This study allows the opportunity to determine if MORAb-003 can work either as a single agent or in combination with standard platinum and taxane chemotherapy in the setting of minimal disease to a) treat a CA125-only relapse, or b) to prolong a second response to chemotherapy in the setting of relapsed platinum-sensitive subjects.
MORAb-003 is a humanized IgG1* produced in CHO cells. MORAb-003 binds to the folate receptor alpha (FRA), which is over expressed in virtually all epithelial ovarian cancer cells, including primary peritoneal and fallopian tube malignancies. The expression of FRA is known to relate to the malignant potential of the cancer. MORAb-003 is effective in preclinical xenograft models of ovarian cancer, in addition to being very active in antibody-dependent cellular cytotoxicity (ADCC) assays. MORAb-003 has been shown to inhibit phosphorylation of proteins by the Lyn kinase (a member of the src family of kinases) and to inhibit the growth of FRA-expressing cells in low folate conditions.
MORAb-003 was given to cynomolgus monkeys in three studies; a dose-ranging study of 15 days duration, a GLP toxicity study of 28 days duration and second

GLP study of 6 months duration. There were no specific toxicities identified, and no maximum tolerated dose was identified.
1.2 Summary of clinical data
MORAb-003 has been used in a single phase 1 study in humans with platinum resistant or refractory epithelial ovarian cancer. As of the 37.5 mg/m2 dose group, no significant related adverse events had been seen, and testing of higher dose groups is ongoing. Two subjects had stable disease by RECIST criteria over the course of the study, and one of these subjects had a 20% decrease in CA125. Isolated drug fever without any symptoms or signs of histamine release (i.e. no signs of anaphylaxis) was observed in two subjects. One subject with pre-existing dermatomyositis had a facial rash that resolved. Pharmacokinetic analysis in this group of high-disease burden and low dose subjects demonstrated a shorter-than expected half life. There was no evidence of human anti-human antibody formation. This phenomenon has been observed in several biological drugs and may represent tumor binding of the drug. Additional studies are underway to further investigate pharmacokinetics and tumor binding characteristics.

Study objective

The objective of this study is to determine the efficacy of multiple intravenous infusions of MORAb-003 in platinum-sensitive subjects with a first relapse of epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) within 6 to 18 months of first remission. The efficacy will be determined in three settings:

As a single agent in asymptomatic subjects with an increased CA125 (with or without measurable disease) to achieve a response in CA125 and/or measurable tumor burden;

In combination with standard (platinum with or without taxane) chemotherapy to improve the response rate (relative to historical control) of chemotherapy to induce second response
- In asymptomatic subjects after single-agent MORAb-003
- In subjects who relapse with symptoms or disease burden that requires standard (platinum with or without taxane) chemotherapy;

As single-agent maintenance therapy to prolong the second response in subjects who achieve a CR or PR (or SD and an investigator*s assessment of a clinical benefit) after MORAb-003 in combination with standard chemotherapy.

Study design

Subjects with EOC who are experiencing their first relapse may enter the study. The original chemotherapy must have been a standard regimen of intravenous or intraperitoneal platinum with or without taxane, and they must

be a candidate to receive the same chemotherapy again to induce a second response. (If the subject received taxane in the original chemotherapy but is unable to take additional taxane due to side effects, she is still eligible to participate in this study.) No new agents may be added to the original chemotherapy regimen, although substitutions of materially similar agents are permissible.
The first remission must be of 6 to 18 months duration.
The relapse will be classified as *non-symptomatic* or *symptomatic* and the subjects assigned to different treatment arms accordingly. Subjects without symptoms may be assigned to the *symptomatic* treatment arm based on the investigator*s assessment of the subject*s immediate need for standard chemotherapy.

Non-symptomatic relapses will include those relapses that are defined only by an increase in CA125, with or without measurable disease by imaging, physical exam, or other techniques. An increase in CA125 will be defined as a doubling of the level, measured at two time points at least one week apart, and the level must be at least 35 kU/L, according to a modification of the GCIG criteria. Non-symptomatic subjects will receive 9 weeks of MORAb-003, followed by a disease reassessment and standard chemotherapy consisting of a repeat of their original regimen, plus MORAb-003.
If there is a clear response in both CA125 and any measurable disease (if present) standard chemotherapy may be withheld and the subject treated with continued MORAb-003 as decided on a case by case basis by the investigator and the sponsor*s medical expert. Continuing subjects will follow the same study schedule as described for the first 9 weeks.

Symptomatic relapses will include any relapses that, in the opinion of the investigator, require standard therapy sooner than 9 weeks due to the presence of symptoms (e.g. significant ascites, actual or impending bowel obstruction), or lesions of a size or characteristic that in the normal practice of oncology require standard cytotoxic therapy. These subjects will receive standard chemotherapy plus MORAb-003.

Subjects from either arm (non-symptomatic or symptomatic) will receive standard chemotherapy with added MORAb-003. Standard chemotherapy will mimic as closely as possible that subject*s original regimen, which typically will have consisted of platinum (cis-platinum or carboplatin) and a taxane (paclitaxel or docetaxel). In addition, MORAb-003 will be administered. Usually six courses of platinum/taxane will be administered, but fewer or more may be used if in the opinion of the investigator it is in the subject*s best interest. If a CR or PR (or SD and an investigator*s assessment of a clinical benefit) is achieved, the subject will be treated with MORAb-003 as a single agent to maintain the response.

Intervention

MORAb-003 is a humanized IgG1/* monoclonal antibody that binds to the human folate alpha receptor. MORAb-003 is 99.15% humanized.
The dose of investigational product required for a subject is to be taken from as many vials as required. Remaining study medication left in a vial after withdrawing the subject's assigned dose is not to be used for subsequent doses. Study drug will be fully accounted for.
A fine translucent or white precipitate may be seen in the vials of MORAb-003. A 0.22 micron in-line filter should be used. In order to ensure that the subject receives the full dose of MORAb-003, the tubing should be flushed with a volume of normal saline sufficient to deliver the drug substance remaining in the tubing.
Each dose of investigational product will be given as a continuous infusion. Subjects should receive MORAb-003 initially at 1-2 mg/min and the rate progressed as tolerated. If no Grade 2 or greater infusion reactions are encountered, subsequent doses may be given at a higher rate. The rate should be increased at increments of 2 mg/min, no more than every 15 minutes. If infusion-related adverse effects are encountered, the infusion rate should be decreased by at least 50%, and then advanced back to the highest rate that was well-tolerated.
MORAb-003 administration will be strictly intravenous. If an indwelling venous access device is used, MORAb-003 will be administered via a different lumen than that used for blood collections whenever possible. It is recommended that MORAb-003 be administered via the most distal lumen of a multi-lumen catheter to reduce the possibility of confounding pharmacokinetic analyses.

Study burden and risks

This is the first phase 2 study of MORAb-003. Up to a level of 62.5 mg/m2 weekly infusions, no significant drug-related adverse events have been demonstrated other than isolated drug fever as noted. Phase 1 studies are still ongoing to identify if any drug-related adverse events will be identified at higher doses. Investigators and IRBs associated with this study will be informed immediately if any new safety information is found in relation to MORAb-003. Preclinical studies have not identified any specific risks to date. In general, administration of monoclonal antibodies can cause allergic or anaphylactic reactions. Also, the antibodies may bind specifically or non-specifically to antigens expressed on non-tumor tissue which could ensue in a reaction.
In the phase 1 study, two subjects with short term exposure had radiographically stable disease over 35 days. One of the subjects had a 20% decrease in CA125 that did not meet the Rustin criteria for response due to the short time of follow-up. There are no other known benefits of MORAb-003.

Contacts

Public
Morphotek, Inc

210 Welsh Pool Road
Exton, PA 19341
Verenigde Staten
Scientific
Morphotek, Inc

210 Welsh Pool Road
Exton, PA 19341
Verenigde Staten

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Female subjects, * 18 years of age, with a histologically confirmed diagnosis of non-mucinous epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) in first relapse after a first remission of 6 to 18 months duration.
2. Subjects must have undergone surgery. Subjects must have received primary chemotherapy, including at least one platinum agent.
3. Subject is eligible for retreatment with the same chemotherapy regimen that was used to induce remission (Exception: may reduce the dose of or discontinue taxane if contraindicated due to neurotoxicity.)
4. CA125 must have been elevated prior to original chemotherapy.
5. CA125 must be elevated at the time of relapse.
6. Life expectancy * 6 months, as estimated by the investigator.
7. Eastern Cooperative Oncology Group performance status or 0, 1 or 2 (see Appendix D).

8. Subjects must consent to use a medically acceptable method of contraception throughout the study period and for 28 days after final MORAb-003 administration, unless surgically sterile.
9. Any significant concomitant medical conditions must be well controlled and stable in the opinion of the investigator for at least 30 days prior to Study Day 1.
10. Laboratory and clinical results within the 2 weeks prior to Study Day 1 as follows:
Absolute neutrophil count (ANC) * 1.2 x 109/L
Platelet count * 100 x 109/L
Hemoglobin * 8 g/dL
13. Subject must be willing and able to provide written informed consent. Translations of informed consent information may be provided, subject to the local IRB*s policy.

Exclusion criteria

1. Known central nervous system (CNS) tumor involvement.
2. Evidence of other active malignancy requiring treatment.
3. Clinically significant heart disease (e.g., congestive heart failure of New York Heart Association Class III or IV, angina not well controlled by medication, or myocardial infarction within 6 months).
4. ECG demonstrating clinically significant arrhythmias (Exception: Subjects with chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal SVT, are eligible).
5. Active serious systemic disease, including active bacterial or fungal infection.
6. Active hepatitis or HIV infection.
7. Treatment within three months with immunomodulatory therapy (e.g. interferons, immunoglobulin therapy, IL-1RA or systemic corticosteroids). Short term systemic corticosteroids or topical or intra-articular steroids are acceptable, subject to the judgment of the investigator.
8. Treatment with a monoclonal antibody therapy AND have evidence of an immune or allergic reaction or documented HAHA.
9. Maintenance of first remission by taxane or other chemotherapeutic agent(s).
10. Initiation or planned initiation of cancer therapy not given to induce primary remission. Substitutions of agents materially similar to those used in the original regimen are permissible.
11. Breast-feeding, pregnant, or likely to become pregnant during the study.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2007
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MORAb-003
Generic name:	MORAb-003

Ethics review

Approved WMO Date:	19-09-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-003580-31-NL
ClinicalTrials.gov	NCT00318370
CCMO	NL13398.029.07